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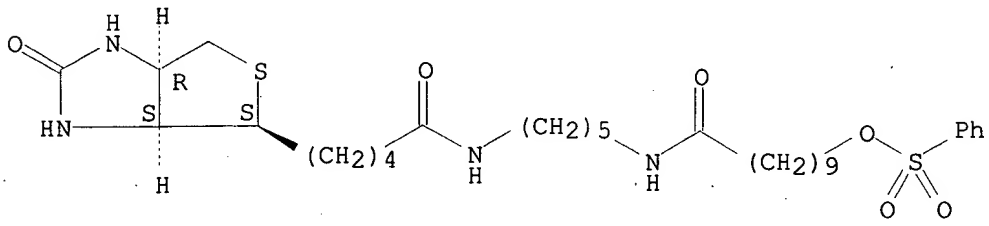
L17 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN **342792-18-1** REGISTRY
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-2-oxo-N-[5-[[1-oxo-10-[(phenylsulfonyl)oxy]decyl]amino]pentyl]-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H50 N4 O6 S2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1937 TO DATE)
4 REFERENCES IN FILE CAPLUS (1937 TO DATE)

4 hits from "specific example"

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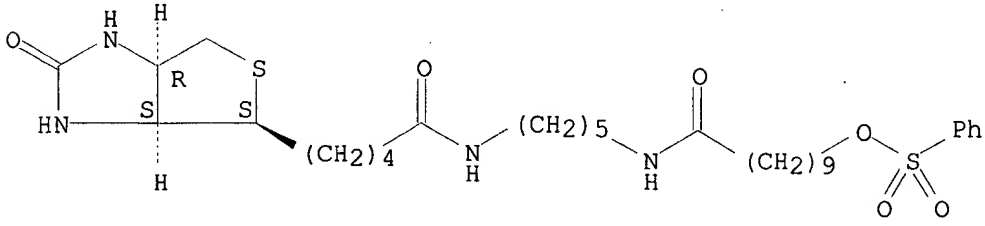
L18 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:564598 HCAPLUS
DOCUMENT NUMBER: 138:182893
TITLE: Proteomic profiling of mechanistically distinct enzyme classes using a common chemotype
AUTHOR(S): Adam, Gregory C.; Sorensen, Erik J.; Cravatt, Benjamin F.
CORPORATE SOURCE: The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Nature Biotechnology (2002), 20(8), 805-809
CODEN: NABIF9; ISSN: 1087-0156
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Proteomics research requires methods to characterize the expression and function of proteins in complex mixts. Toward this end, chem. probes that incorporate known affinity labeling agents have facilitated the activity-based profiling of certain enzyme families. To accelerate the discovery of proteomics probes for enzyme classes lacking cognate affinity labels, we describe here a combinatorial strategy. Members of a probe library bearing a sulfonate ester chemotype were screened against complex proteomes for activity-dependent protein reactivity, resulting in the labeling of at least six mechanistically distinct enzyme classes. Surprisingly, none of these enzymes represented targets of previously described proteomics probes. The sulfonate library was used to identify an omega-class glutathione S-transferase whose activity was upregulated in invasive human breast cancer lines. These results indicate that activity-based probes compatible with whole-proteome anal. can be developed for numerous enzyme classes and applied to identify enzymes assocd. with discrete pathol. states.
IT **342792-18-1**
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(proteomic profiling of mechanistically distinct enzyme classes using a common chemotype)
RN 342792-18-1 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-2-oxo-N-[5-[[1-oxo-10-[(phenylsulfonyl)oxy]decyl]amino]pentyl]-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:763323 HCAPLUS
DOCUMENT NUMBER: 135:315598
TITLE: Methods for proteomic analysis using activity based probes for target proteins
INVENTOR(S): Cravatt, Benjamin F.; Sorensen, Erik; Patricelli, Matthew; Lovato, Martha; Adam, Gregory
PATENT ASSIGNEE(S): Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077684	A2	20011018	WO 2000-US34187	20001215
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002045194	A1	20020418	US 2000-738954	20001215
EP 1275006	A2	20030115	EP 2000-990226	20001215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002040275	A1	20020404	US 2001-836148	20010416
US 2002064799	A1	20020530	US 2001-836145	20010416
US 2002182652	A1	20021205	US 2002-158498	20020529

PRIORITY APPLN. INFO.:

US 2000-195954P	P	20000410
US 2000-212891P	P	20000620
US 2000-222532P	P	20000802
US 2000-738271	A1	20001215
US 2000-738954	A1	20001215
WO 2000-US34187	W	20001215

OTHER SOURCE(S): MARPAT 135:315598

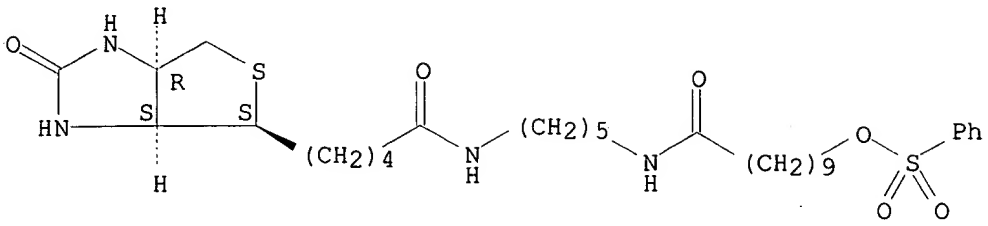
AB The present invention provides methods for analyzing proteomes, as cells or lysates. The anal. is based on the use of probes that have specificity to the active form of proteins, particularly enzymes and receptors. The probes can be identified in different ways. In accordance with the present invention, a method is provided for generating and screening compd. libraries that are used for the identification of lead mols., and for the parallel identification of their biol. targets. By appending specific functionalities and/or groups to one or more binding moieties, the reactive functionalities gain binding affinity and specificity for particular proteins and classes of proteins. Such libraries of candidate compds., referred to herein as activity-based probes, or ABPs, are used to screen for one or more desired biol. activities or target proteins.

IT **342792-18-1P**
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(methods for proteomic anal. using activity based probes for target proteins)

RN 342792-18-1 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-2-oxo-N-[5-[[1-oxo-10-[(phenylsulfonyl)oxy]decyl]amino]pentyl]-, (3aS,4S,6aR)- (9CI) (CA INDEX

NAME)

Absolute stereochemistry.



L18 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:763309 HCAPLUS
DOCUMENT NUMBER: 135:315597
TITLE: Methods for bioactivity screening of candidate compounds using activity based probes
INVENTOR(S): Cravatt, Benjamin F.; Sorensen, Erik; Patricelli, Matthew; Lovato, Martha; Adam, Gregory
PATENT ASSIGNEE(S): Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077668	A2	20011018	WO 2000-US34167	20001215
WO 2001077668	A3	20020606		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002045194	A1	20020418	US 2000-738954	20001215
US 2002040275	A1	20020404	US 2001-836148	20010416
US 2002064799	A1	20020530	US 2001-836145	20010416
US 2002182652	A1	20021205	US 2002-158498	20020529

PRIORITY APPLN. INFO.:
US 2000-195954P P 20000410
US 2000-212891P P 20000620
US 2000-222532P P 20000802
US 2000-738271 A1 20001215
US 2000-738954 A1 20001215

OTHER SOURCE(S): MARPAT 135:315597

AB The present invention provides methods for analyzing proteomes, as cells or lysates. The anal. is based on the use of probes that have specificity to the active form of proteins, particularly enzymes and receptors. The probes can be identified in different ways. In accordance with the present invention, a method is provided for generating and screening compd. libraries that are used for the identification of lead mols., and for the parallel identification of their biol. targets. By appending

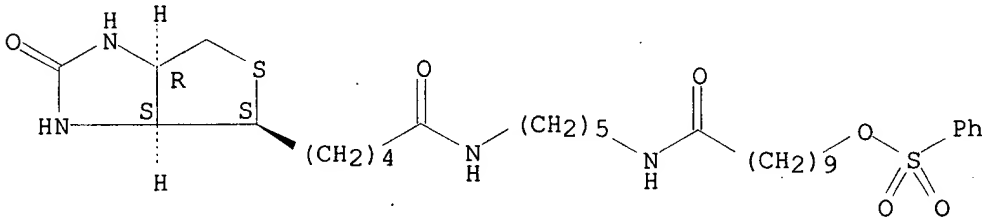
specific functionalities and/or groups to one or more binding moieties, the reactive functionalities gain binding affinity and specificity for particular proteins and classes of proteins. Such libraries of candidate compds., referred to herein as activity-based probes, or ABPs, are used to screen for one or more desired biol. activities or target proteins.

IT **342792-18-1P**
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(methods for bioactivity screening of candidate compds. using activity based probes)

RN 342792-18-1 HCAPLUS

CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-2-oxo-N-[5-[[1-oxo-10-[(phenylsulfonyl)oxy]decyl]amino]pentyl]-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L18 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:175793 HCAPLUS

DOCUMENT NUMBER: 135:16295

TITLE: Profiling the specific reactivity of the proteome with non-directed activity-based probes

AUTHOR(S): Adam, Gregory C.; Cravatt, Benjamin F.; Sorensen, Erik J.

CORPORATE SOURCE: The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA

SOURCE: Chemistry & Biology (2001), 8(1), 81-95
CODEN: CBOLE2; ISSN: 1074-5521

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 135:16295

AB Background: The field of proteomics aims to characterize dynamics in protein function on a global level. However, several classes of proteins, in particular low abundance proteins, remain difficult to characterize using std. proteomics technologies. Recently, chem. strategies have emerged that profile classes of proteins based on activity rather than quantity, thereby greatly facilitating the anal. of low abundance constituents of the proteome. Results: In order to expand the classes of proteins susceptible to anal. by activity-based methods, we have synthesized a library of biotinylated sulfonate esters and applied its members to complex proteomes under conditions that distinguish patterns of specific protein reactivity. Individual sulfonates exhibited unique profiles of proteome reactivity that in extreme cases appeared nearly orthogonal to one another. A robustly labeled protein was identified as a class I aldehyde dehydrogenase and shown to be irreversibly inhibited by members of the sulfonate library. Conclusions: Through screening the proteome with a nondirected library of chem. probes, diverse patterns of

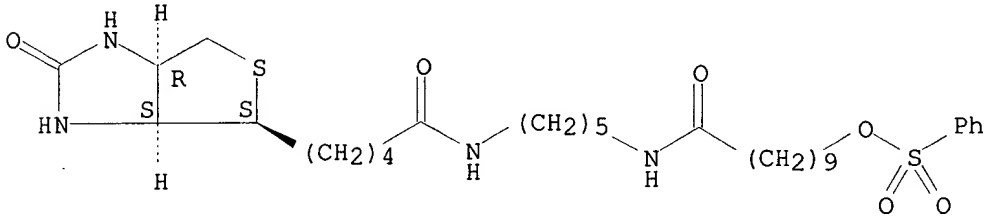
protein reactivity were uncovered. These probes labeled protein targets based on properties other than abundance, circumventing one of the major challenges facing contemporary proteomics research. Considering further that the probes were found to inhibit a target enzyme's catalytic activity, the methods described herein should facilitate the identification of compds. possessing both selective proteome reactivities and novel bioactivities.

IT **342792-18-1P**
RL: ARG (Analytical reagent use); ARU (Analytical role, unclassified); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(profiling specific reactivity of proteome with non-directed activity-based probes)

RN 342792-18-1 HCAPLUS

CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-2-oxo-N-[5-[[1-oxo-10-[(phenylsulfonyl)oxy]decyl]amino]pentyl]-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L4          2338 SEA FILE=REGISTRY ABB=ON  L3 AND 46.150.18/RID
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L9            49 SEA FILE=REGISTRY ABB=ON  L7 AND NR>1 AND NRS>1
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L23  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER:         2002:899767  HCAPLUS
DOCUMENT NUMBER:          138:250529
TITLE:                    Trifunctional chemical probes for the consolidated
                          detection and identification of enzyme activities from
                          complex proteomes
AUTHOR(S):                Adam, Gregory C.; Sorensen, Erik J.; Cravatt, Benjamin
                          F.
CORPORATE SOURCE:         The Skaggs Institute for Chemical Biology and the
                          Department of Chemistry, The Scripps Research
                          Institute, La Jolla, CA, 92037, USA
SOURCE:                   Molecular and Cellular Proteomics (2002), 1(10),
                          828-835
                          CODEN: MCPOBS; ISSN: 1535-9476
PUBLISHER:                American Society for Biochemistry and Molecular
                          Biology, Inc.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB    Chem. probes that covalently modify the active sites of enzymes in complex
      proteomes are useful tools for identifying enzyme activities assocd. with
      discrete (patho)physiol. states. Researchers in proteomics typically use
      two types of activity-based probes to fulfill complementary objectives:
      fluorescent probes for rapid and sensitive target detection and
      biotinylated probes for target purifn. and identification. Accordingly,
      we hypothesized that a strategy in which the target detection and target
      isolation steps of activity-based proteomic expts. were merged might
      accelerate the characterization of differentially expressed
      protein activities. Here we report the synthesis and application of
      trifunctional chem. proteomic probes in which elements for both target
      detection (e.g. rhodamine) and isolation (e.g. biotin) are appended to a
      sulfonate ester reactive group, permitting the consolidated visualization
      and affinity purifn. of labeled proteins by a combination of in-gel
      fluorescence and avidin chromatog. procedures. A trifunctional Ph
      sulfonate probe was used to identify several tech. challenging protein
      targets, including the integral membrane enzyme 3.beta.-hydroxysteroid
      dehydrogenase/.DELTA.5-isomerase and the cofactor-dependent
      enzymes platelet-type phosphofructokinase and type II tissue
      transglutaminase. The latter two enzyme activities were significantly
      up-regulated in the invasive estrogen receptor-neg. (ER(-)) human breast
      cancer cell line MDA-MB-231 relative to the non-invasive ER(+) breast
      cancer lines MCF7 and T-47D. Collectively these studies demonstrate that
      chem. proteomic probes incorporating elements for both target detection
      and target isolation fortify the important link between the visualization
      of differentially expressed enzyme activities and their
      subsequent mol. identification, thereby augmenting the information content
```

achieved in activity-based profiling expts.

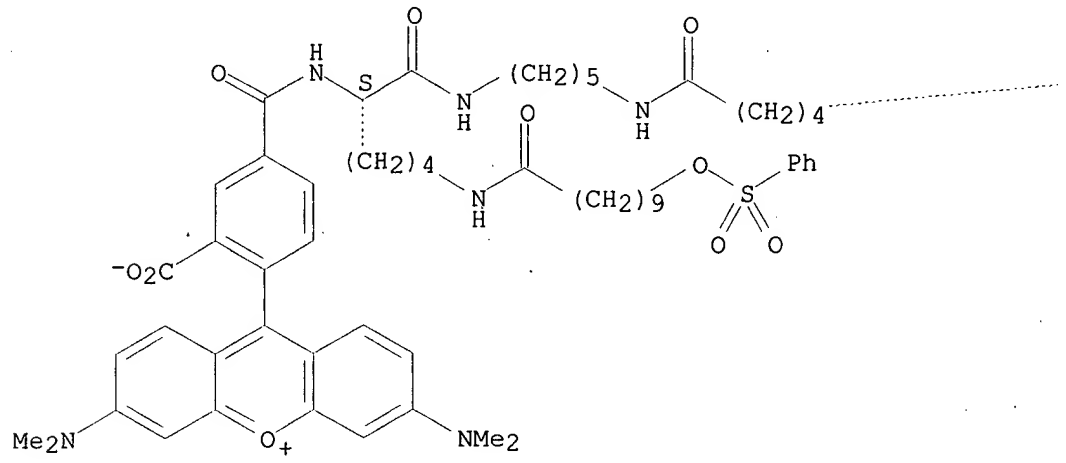
IT **501131-76-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(trifunctional chem. probes combine detection and identification of enzyme activities from complex proteomes)

RN 501131-76-6 HCAPLUS

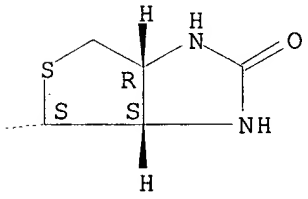
CN Xanthylium, 9-[2-carboxy-4-[[[(1S)-1-[[[5-[[5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]pentyl]amino]carbonyl]-5-[[1-oxo-10-[(phenylsulfonyl)oxy]decyl]amino]pentyl]amino]carbonyl]phenyl]-3,6-bis(dimethylamino)-, inner salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

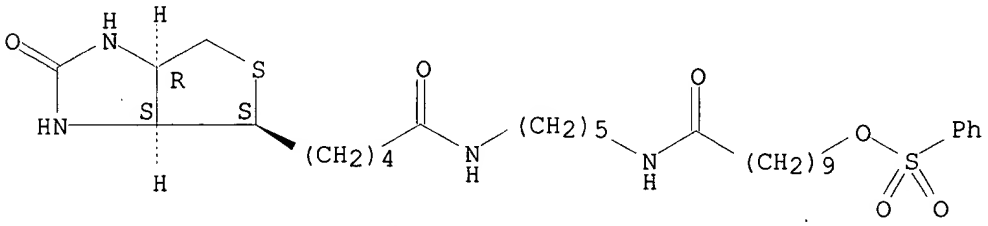
L23 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:564598 HCAPLUS
DOCUMENT NUMBER: 138:182893
TITLE: Proteomic profiling of mechanistically distinct enzyme classes using a common chemotype
AUTHOR(S): Adam, Gregory C.; Sorensen, Erik J.; Cravatt, Benjamin F.
CORPORATE SOURCE: The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research

Institute, La Jolla, CA, 92037, USA
SOURCE: Nature Biotechnology (2002), 20(8), 805-809
CODEN: NABIF9; ISSN: 1087-0156
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Proteomics research requires methods to characterize the **expression** and function of proteins in complex mixts. Toward this end, chem. probes that incorporate known affinity labeling agents have facilitated the activity-based profiling of certain enzyme families. To accelerate the discovery of proteomics probes for enzyme classes lacking cognate affinity labels, we describe here a combinatorial strategy. Members of a probe library bearing a sulfonate ester chemotype were screened against complex proteomes for activity-dependent protein reactivity, resulting in the labeling of at least six mechanistically distinct enzyme classes. Surprisingly, none of these enzymes represented targets of previously described proteomics probes. The sulfonate library was used to identify an omega-class glutathione S-transferase whose activity was upregulated in invasive human breast cancer lines. These results indicate that activity-based probes compatible with whole-proteome anal. can be developed for numerous enzyme classes and applied to identify enzymes assocd. with discrete pathol. states.

IT **342792-18-1**
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(proteomic profiling of mechanistically distinct enzyme classes using a common chemotype)
RN 342792-18-1 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-2-oxo-N-[5-[[1-oxo-10-[(phenylsulfonyl)oxy]decyl]amino]pentyl]-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:505740 HCAPLUS
DOCUMENT NUMBER: 137:195720
TITLE: Involvement of the second extracellular loop (E2) of the neurokinin-1 receptor in the binding of substance P: Photoaffinity labeling and modeling studies
AUTHOR(S): Lequin, Olivier; Bolbach, Gerard; Frank, Fabrice; Convert, Odile; Girault-Lagrange, Sophie; Chassaing, Gerard; Lavielle, Solange; Sagan, Sandrine
CORPORATE SOURCE: Unite Mixte de Recherches 7613 CNRS, Universite Paul et Marie Curie, Paris, 75252, Fr.
SOURCE: Journal of Biological Chemistry (2002), 277(25), 22386-22394

CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Substance P (SP) interacts with the neurokinin-1 (NK-1) G-protein-coupled receptor, which has been cloned in several species. In the present study, the domains of the NK-1 receptor involved in the binding of SP and SP-(7-11) C-terminal fragment have been analyzed using two peptide analogs contg. the photoreactive amino acid para-benzoylphenylalanine ((p-Bz)Phe) in position 8 of their sequence. This study was carried out with [BAPA-Lys6,(p-Bz)Phe8,-Pro9,Met(O2)11]SP-(7-11) and [BAPA0,(p-Bz)Phe8]SP on both **rat** and human NK-1 receptors **expressed** in CHO cells. Combined trypsin and endo-GluC enzymic complete digestions and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry anal. led to the identification of the same domain of covalent interaction, 173TMPSR177, for the two photo-activatable peptides. Further digestion of this fragment with carboxypeptidase Y led to the identification of 173TMP175 in the second extracellular loop (E2) of the NK-1 receptor as the site of covalent attachment. Models of the conformation of this E2 loop in the human NK-1 receptor were generated using two different strategies, one based on homol. with bovine rhodopsin and the other based on the soln. conformation preferences of a synthetic peptide corresponding to the E2 loop.

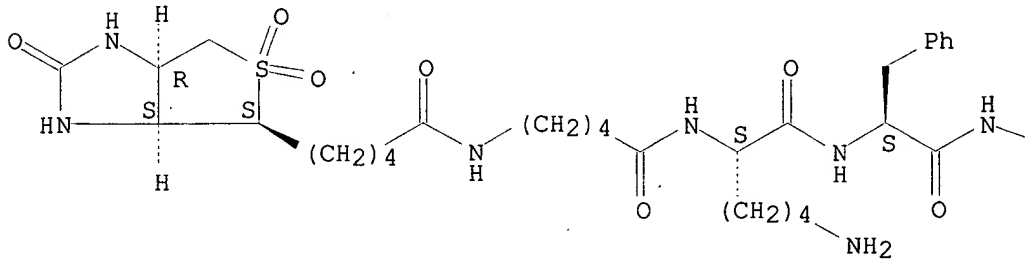
IT **454234-21-0**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(neurokinin-1 receptor second extracellular loop in binding of substance P from photoaffinity labeling and modeling studies)

RN 454234-21-0 HCAPLUS

CN Butanamide, N2-[5-[[5-[(3aS,4S,6aR)-hexahydro-5,5-dioxido-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]-1-oxopentyl]-L-lysyl-L-phenylalanyl-4-benzoyl-L-phenylalanyl-L-prolyl-L-leucyl-2-amino-4-(methylsulfonyl)-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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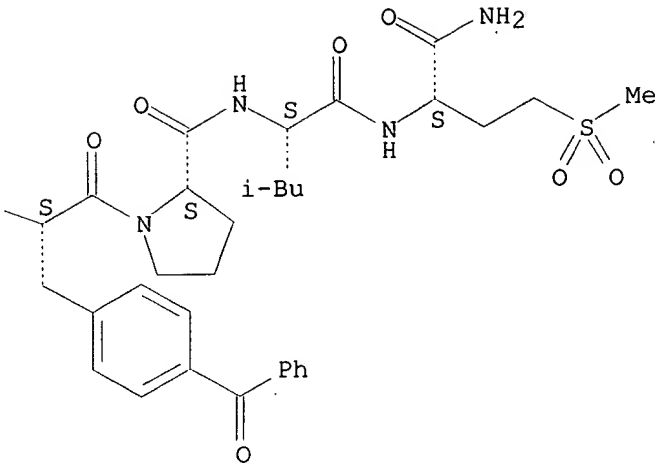


REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:763323 HCAPLUS
DOCUMENT NUMBER: 135:315598
TITLE: Methods for proteomic analysis using activity based probes for target proteins
INVENTOR(S): Cravatt, Benjamin F.; Sorensen, Erik; Patricelli, Matthew; Lovato, Martha; Adam, Gregory
PATENT ASSIGNEE(S): Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077684	A2	20011018	WO 2000-US34187	20001215
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 2002045194	A1	20020418	US 2000-738954	20001215
EP 1275006	A2	20030115	EP 2000-990226	20001215
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
US 2002040275	A1	20020404	US 2001-836148	20010416
US 2002064799	A1	20020530	US 2001-836145	20010416
US 2002182652	A1	20021205	US 2002-158498	20020529
PRIORITY APPLN. INFO.:			US 2000-195954P P	20000410
			US 2000-212891P P	20000620

US 2000-222532P P 20000802
US 2000-738271 A1 20001215
US 2000-738954 A1 20001215
WO 2000-US34187 W 20001215

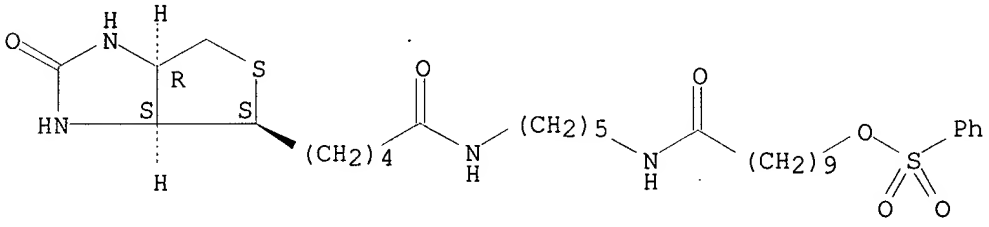
OTHER SOURCE(S): MARPAT 135:315598

AB The present invention provides methods for analyzing proteomes, as cells or lysates. The anal. is based on the use of probes that have specificity to the active form of proteins, particularly enzymes and receptors. The probes can be identified in different ways. In accordance with the present invention, a method is provided for generating and screening compd. libraries that are used for the identification of lead mols., and for the parallel identification of their biol. targets. By appending specific functionalities and/or groups to one or more binding moieties, the reactive functionalities gain binding affinity and specificity for particular proteins and classes of proteins. Such libraries of candidate compds., referred to herein as activity-based probes, or ABPs, are used to screen for one or more desired biol. activities or target proteins.

IT **342792-18-1P 342792-19-2P**
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(methods for proteomic anal. using activity based probes for target proteins)

RN 342792-18-1 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-2-oxo-N-[5-[[1-oxo-10-[(phenylsulfonyl)oxy]decyl]amino]pentyl]-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

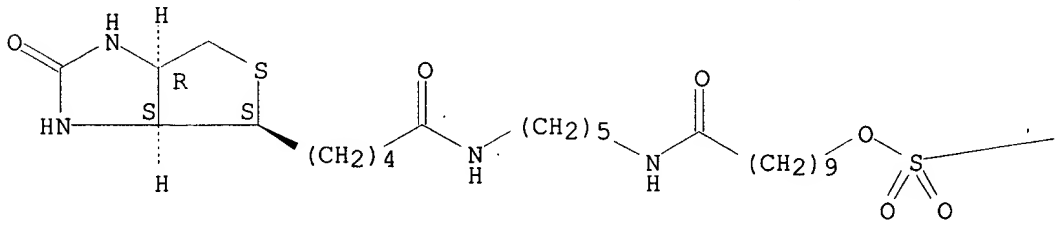
Absolute stereochemistry.

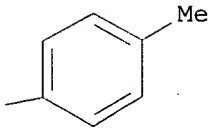


RN 342792-19-2 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-N-[5-[[10-[[(4-methylphenyl)sulfonyl]oxy]-1-oxodecyl]amino]pentyl]-2-oxo-, (3aS,4S,6aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





L23 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:763309 HCAPLUS
DOCUMENT NUMBER: 135:315597
TITLE: Methods for bioactivity screening of candidate compounds using activity based probes
INVENTOR(S): Cravatt, Benjamin F.; Sorensen, Erik; Patricelli, Matthew; Lovato, Martha; Adam, Gregory
PATENT ASSIGNEE(S): Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077668	A2	20011018	WO 2000-US34167	20001215
WO 2001077668	A3	20020606		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002045194	A1	20020418	US 2000-738954	20001215
US 2002040275	A1	20020404	US 2001-836148	20010416
US 2002064799	A1	20020530	US 2001-836145	20010416
US 2002182652	A1	20021205	US 2002-158498	20020529

PRIORITY APPLN. INFO.:
US 2000-195954P P 20000410
US 2000-212891P P 20000620
US 2000-222532P P 20000802
US 2000-738271 A1 20001215
US 2000-738954 A1 20001215

OTHER SOURCE(S): MARPAT 135:315597

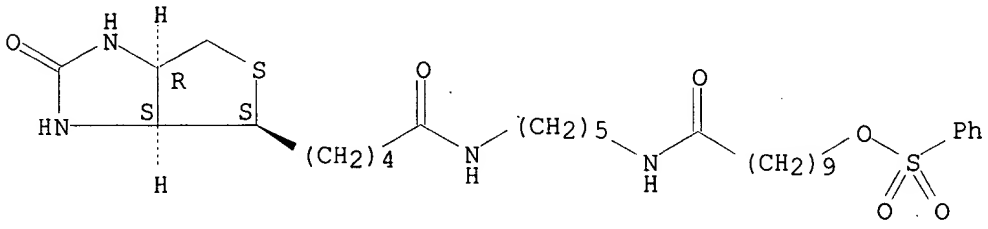
AB The present invention provides methods for analyzing proteomes, as cells or lysates. The anal. is based on the use of probes that have specificity to the active form of proteins, particularly enzymes and receptors. The probes can be identified in different ways. In accordance with the present invention, a method is provided for generating and screening compd. libraries that are used for the identification of lead mols., and for the parallel identification of their biol. targets. By appending specific functionalities and/or groups to one or more binding moieties, the reactive functionalities gain binding affinity and specificity for particular proteins and classes of proteins. Such libraries of candidate compds., referred to herein as activity-based probes, or ABPs, are used to

screen for one or more desired biol. activities or target proteins.

IT **342792-18-1P 342792-19-2P**
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(methods for bioactivity screening of candidate compds. using activity based probes)

RN 342792-18-1 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-2-oxo-N-[5-[[1-oxo-10-[(phenylsulfonyl)oxy]decyl]amino]pentyl]-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

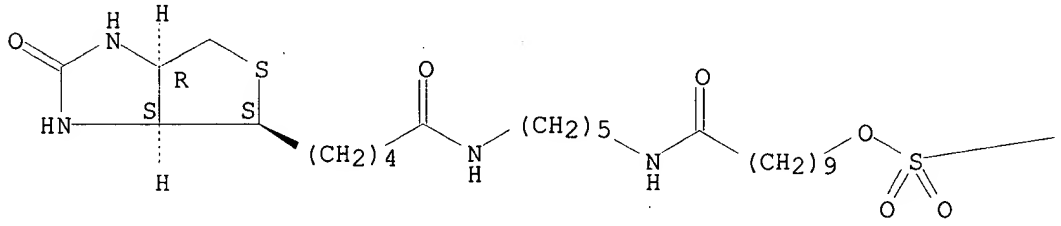
Absolute stereochemistry.



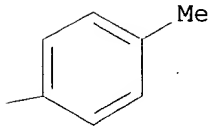
RN 342792-19-2 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-N-[5-[[10-[[(4-methylphenyl)sulfonyl]oxy]-1-oxodecyl]amino]pentyl]-2-oxo-, (3aS,4S,6aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L23 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:175793 HCAPLUS
DOCUMENT NUMBER: 135:16295
TITLE: Profiling the specific reactivity of the proteome with non-directed activity-based probes
AUTHOR(S): Adam, Gregory C.; Cravatt, Benjamin F.; Sorensen, Erik J.
CORPORATE SOURCE: The Skaggs Institute for Chemical Biology and

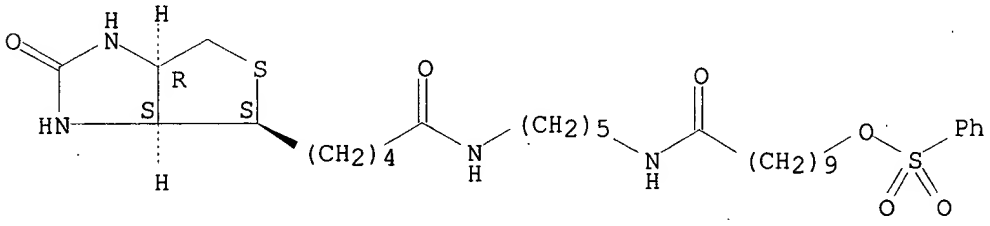
Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Chemistry & Biology (2001), 8(1), 81-95
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:16295

AB Background: The field of proteomics aims to characterize dynamics in protein function on a global level. However, several classes of proteins, in particular low abundance proteins, remain difficult to characterize using std. proteomics technologies. Recently, chem. strategies have emerged that profile classes of proteins based on activity **rather** than quantity, thereby greatly facilitating the anal. of low abundance constituents of the proteome. Results: In order to expand the classes of proteins susceptible to anal. by activity-based methods, we have synthesized a library of biotinylated sulfonate esters and applied its members to complex proteomes under conditions that distinguish patterns of specific protein reactivity. Individual sulfonates exhibited unique profiles of proteome reactivity that in extreme cases appeared nearly orthogonal to one another. A robustly labeled protein was identified as a class I aldehyde **dehydrogenase** and shown to be irreversibly inhibited by members of the sulfonate library. Conclusions: Through screening the proteome with a nondirected library of chem. probes, diverse patterns of protein reactivity were uncovered. These probes labeled protein targets based on properties other than abundance, circumventing one of the major challenges facing contemporary proteomics research. Considering further that the probes were found to inhibit a target enzyme's catalytic activity, the methods described herein should facilitate the identification of compds. possessing both selective proteome reactivities and novel bioactivities.

IT **342792-18-1P 342792-19-2P**
RL: ARG (Analytical reagent use); ARU (Analytical role, unclassified); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(profiling specific reactivity of proteome with non-directed activity-based probes)

RN 342792-18-1 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-2-oxo-N-[5-[[1-oxo-10-[(phenylsulfonyl)oxy]decyl]amino]pentyl]-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

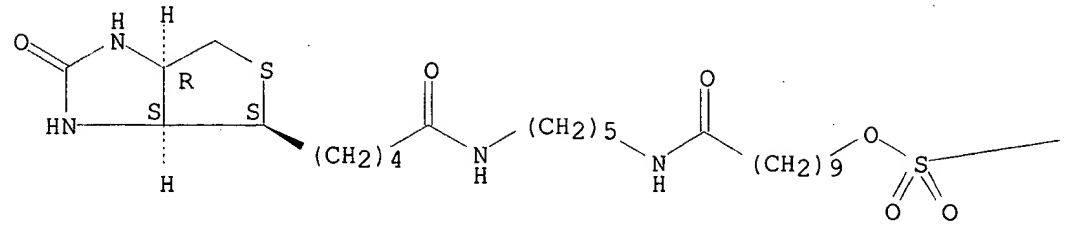
Absolute stereochemistry.



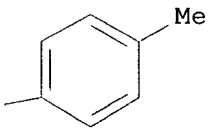
RN 342792-19-2 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-N-[5-[[10-[[(4-methylphenyl)sulfonyl]oxy]-1-oxodecyl]amino]pentyl]-2-oxo-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:433865 HCAPLUS
DOCUMENT NUMBER: 133:248663
TITLE: Evaluation of Biotin-Dye Conjugates for Use in an HPLC Assay To Assess Relative Binding of Biotin Derivatives with Avidin and Streptavidin
AUTHOR(S): Wilbur, D. Scott; Pathare, Pradip M.; Hamlin, Donald K.; Frownfelter, Milah B.; Kegley, Brian B.; Leung, Wai-Yee; Gee, Kyle R.
CORPORATE SOURCE: Department of Radiation Oncology, University of Washington, Seattle, WA, 98195, USA
SOURCE: Bioconjugate Chemistry (2000), 11(4), 584-598
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this investigation, studies were conducted to det. if size exclusion HPLC could be used to assess relative assocn. **rates** (on-**rates**) and dissocn. **rates** (off-**rates**) of biotin derivs. from avidin (Av) and streptavidin (SAv). For easy detection and quantification of biotin derivs., mols. that can be detected by UV absorbance were conjugated to biotin. Concern that conjugation of the chromophoric moieties (dyes) might affect biotin binding with Av and SAv or might interact with the HPLC column led to evaluation of 10 biotin-dye conjugates. The dyes conjugated with biotin included dansyl, cyanocobalamin (CN-Cbl), coumarin 343, Lissamine-rhodamine, fluorescein, Cascade Blue, Lucifer Yellow, Oregon Green, tetramethylrhodamine, and Alexa Fluor 594. The biotin-dye conjugates were initially evaluated to det. their peak characteristics on two different size exclusion HPLC columns. Measurement of the percent of biotin-dye conjugate bound with Av in the presence of an equal quantity of biotin provided an assocn. **rate** relative to biotin. All of the biotin-dyes tested had assocn. **rates** within a factor of 3.times. (slower) that of

biotin. The relative dissocn. **rate** of biotin-dye conjugates was assessed by challenging the biotin conjugate bound to Av or SAv with a large excess of biotin. All of the initial biotin-dye conjugates tested bound Av and SAv tightly resulting in very slow dissocn. **rates**. From the biotin-dye conjugates studied, biotin-CN-Cbl was selected as the best conjugate for the HPLC assay. To test the HPLC assay, an iminobiotin-CN-Cbl conjugate and a biotin-sarcosine-CN-Cbl conjugate were synthesized. The fact that the iminobiotin does not bind with Av at physiol. pH was easily detected in the size exclusion HPLC assay. The biotin-sarcosine-CN-Cbl conjugate was expected to have a more rapid dissocn. **rate** than the other biotin-dye conjugates. This was confirmed in that HPLC assay. Although the biotin-sarcosine-CN-Cbl conjugate bound tightly with Av in the absence of added biotin, it was completely released within 1 h when challenged by an excess of biotin. A slower dissocn. was noted with SAv. The results obtained indicate that CN-Cbl conjugates of biotin derivs. can be used to det. relative on-**rates** and off-**rates** of biotin derivs. with Av and SAv.
The studies also demonstrated that the biotin-CN-Cbl conjugate can be used as a ref. compd. to compare on-**rates** and off-**rates** of nonchromophoric biotin derivs.

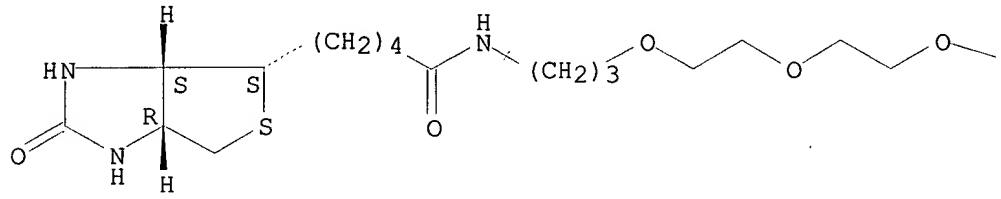
IT **294856-91-0P**
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(evaluation of biotin-dye conjugates for use in HPLC assay to assess relative binding of biotin derivs. with avidin and streptavidin)

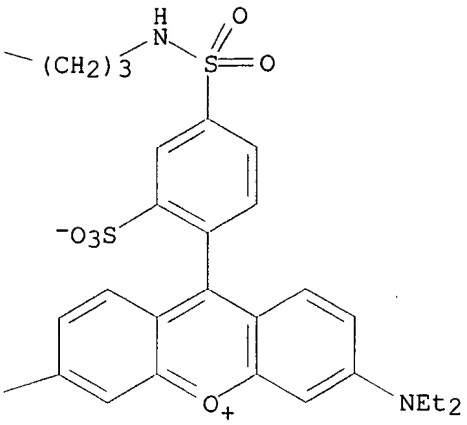
RN 294856-91-0 HCAPLUS

CN Xanthylium, 3,6-bis(diethylamino)-9-[4-[[[19-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-15-oxo-4,7,10-trioxa-14-azanonadec-1-yl]amino]sulfonyl]-2-sulfophenyl]-, inner salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:469925 HCAPLUS
DOCUMENT NUMBER: 125:196372
TITLE: Spiro piperidines which promote release of growth hormone
INVENTOR(S): Chen, Meng-Hsin; Johnston, David B. R.; Nargund, Ravi P.; Patchett, Arthur A.; Tata, James R.; Yang, Lihu
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: U.S., 48 pp., Cont.-in-part of U.S. Ser. No. 989, 322, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5536716	A	19960716	US 1993-147226	19931103
WO 9413696	A1	19940623	WO 1993-US11038	19931115
W: BB, BG, BR, BY, CZ, FI, HU, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ				
RW: BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
WO 9419367	A1	19940901	WO 1993-US11137	19931115
W: BB, BG, BR, BY, CZ, FI, HU, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ				
RW: BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
HU 72076	A2	19960328	HU 1995-1683	19931115
HU 73228	A2	19960729	HU 1995-1681	19931115
PL 176993	B1	19990831	PL 1993-309331	19931115
RU 2168512	C2	20010610	RU 1995-113349	19931115
SK 282166	B6	20011106	SK 1995-759	19931115
CA 2110670	AA	19940612	CA 1993-2110670	19931203
CA 2110670	C	20010417		
CA 2110672	AA	19940612	CA 1993-2110672	19931203
EP 615977	A1	19940921	EP 1993-309867	19931208
EP 615977	B1	20020703		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE

AT	220071	E	20020715	AT 1993-309867	19931208
ES	2177538	T3	20021216	ES 1993-309867	19931208
AU	9352320	A1	19940623	AU 1993-52320	19931210
AU	673552	B2	19961114		
AU	9352321	A1	19940623	AU 1993-52321	19931210
AU	673017	B2	19961024		
ZA	9309272	A	19940808	ZA 1993-9272	19931210
ZA	9309274	A	19940808	ZA 1993-9274	19931210
JP	06263737	A2	19940920	JP 1993-341522	19931210
JP	2509530	B2	19960619		
CN	1092071	A	19940914	CN 1993-112858	19931211
CN	1034733	B	19970430		
FI	9502862	A	19950609	FI 1995-2862	19950609
FI	9502863	A	19950609	FI 1995-2863	19950609
NO	9502294	A	19950810	NO 1995-2294	19950609
NO	9502295	A	19950810	NO 1995-2295	19950609
US	5652235	A	19970729	US 1996-641311	19960430

PRIORITY APPLN. INFO.:	US 1992-989322	B2	19921211
	US 1993-146848		19931103
	US 1993-147226	A	19931103
	WO 1993-US11038	W	19931115
	WO 1993-US11137	W	19931115

OTHER SOURCE(S): MARPAT 125:196372
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB There are disclosed certain novel compds. identified as spiro piperidines and homologs I and II wherein: R1 = e.g., C1-10 alkyl, aryl, aryl-(C1-6 alkyl); R2 = e.g., H, C1-6 alkyl, C3-7 cycloalkyl; R3a and R3b are independently, e.g., H, halo, C1-6 alkyl; R4 and R5 are independently, H, C1-6 alkyl, substituted C1-6 alkyl where the substituents on alkyl are, e.g., 1 to 5 halo, 1 to 3 hydroxy; R6 is H or C1-6 alkyl; A is (CH2)xCR7R7a(CH2)y or Z(CH2)xCR7R7a(CH2)y wherein x and y are independently 0, 1, 2, or 3; Z is NR2 or O; R7 and R7a are independently, e.g., H, C1-6 alkyl, OR2; B, D, E, and F are independently selected from CR8R10, O, CO, SOm, NR9, wherein one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7-membered ring; R8 and R10 are independently, e.g., H, R2, OR2; R9 = e.g., R2, COR2, SO2R2; m is 0, 1, or 2; n is 1 or 2; G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that one or two is a heteroatom, and where one of G, H, I or J may be optionally absent to afford a 5 or 6 membered heterocyclic arom. ring; and the pharmaceutically acceptable salts and individual diastereomers thereof, which promote the release of growth hormone in humans and animals (no data). This property can be utilized to promote the growth of food animals to render the prodn. of edible meat products more efficient, and in humans, to treat physiol. or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compns. contg. such spiro compds. as the active ingredient thereof are also disclosed. Thus, e.g., 1'-(t-butyloxycarbonyl)spiro[1H-indene-1,4'-piperidine] was subjected to hydroboration/oxidn., to provide 1'-(t-butyloxycarbonyl)-2,3-dihydro-3-oxospiro[1H-indene-1,4'-piperidine]; deprotection followed by trifluoroacetylation afforded the trifluoroacetamide; Schmidt reaction of

the latter provided 3,4-dihydro-2-oxospiro[piperidine-4,4'(1H)-quinoline] trifluoroacetamide (together with its spiroisoquinoline isomer); sapon. followed by coupling with .alpha.(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-propanoic acid (prepn. given) and deprotection provided N-[1(R)-[(3,4-dihydro-2-oxospiro[piperidine-4,4'(1H)-quinolin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride (III.HCl).

IT **180466-14-2P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); FFD (Food or feed use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(spiro piperidines which promote release of growth hormone)

RN 180466-14-2 HCAPLUS

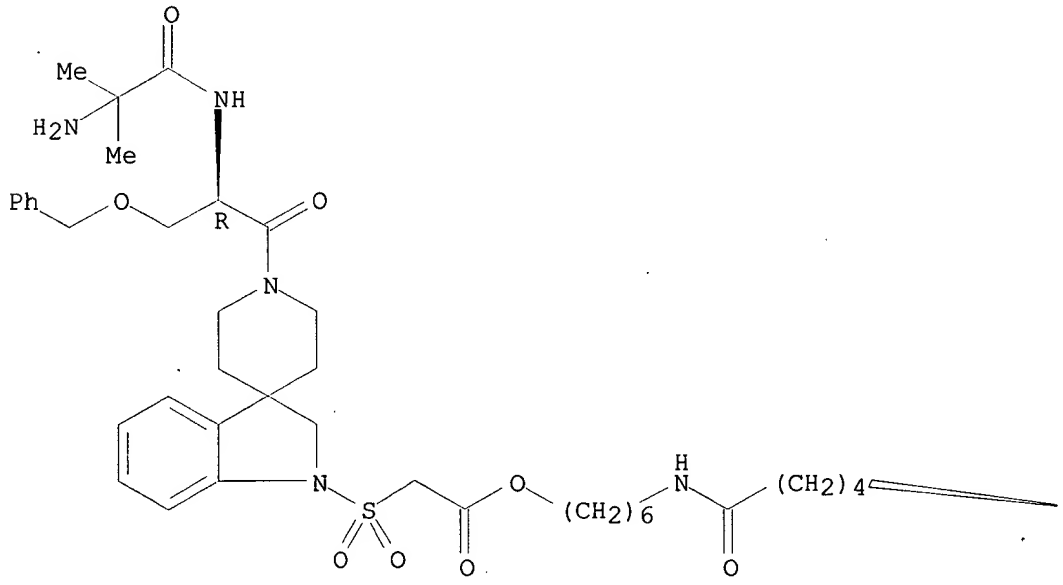
CN Acetic acid, [[1'-[N-(2-methylalanyl)-O-(phenylmethyl)-D-seryl]spiro[3H-indole-3,4'-piperidin]-1(2H)-yl]sulfonyl]-, 6-[[5-(hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl)-1-oxopentyl]amino]hexyl ester, [3aS-(3a.alpha.,4.beta.,6a.alpha.)]-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

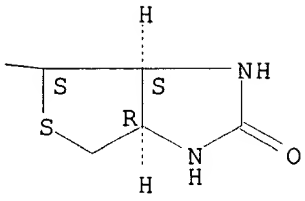
CM 1

CRN 180466-13-1
CMF C44 H63 N7 O9 S2

Absolute stereochemistry.

PAGE 1-A





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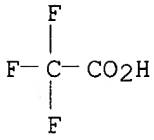
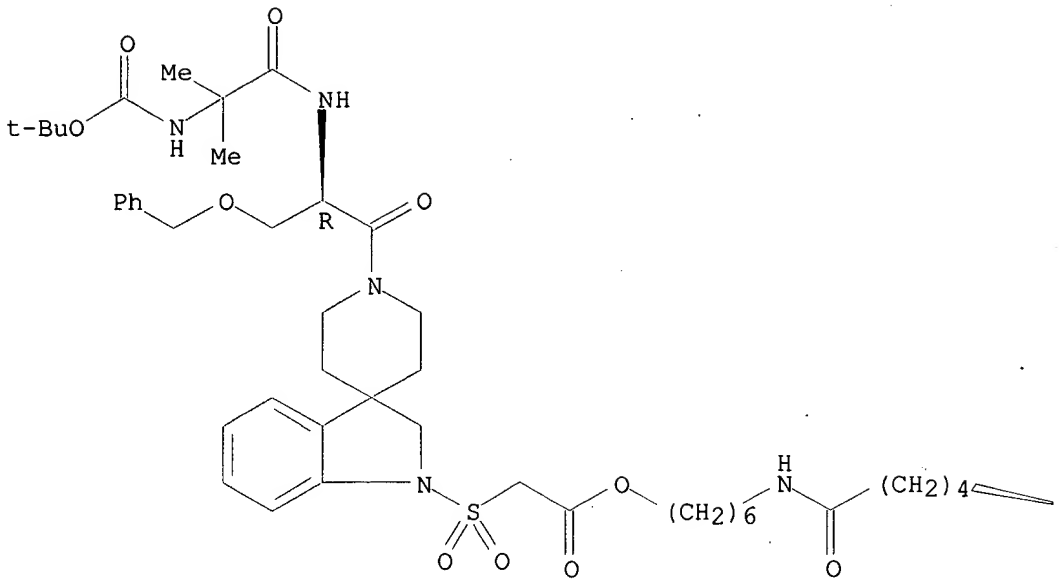


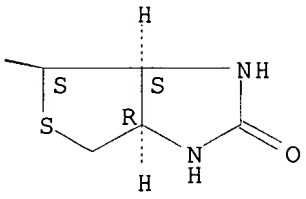
IT **180466-12-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(spiro piperidines which promote release of growth hormone)
RN 180466-12-0 HCAPLUS
CN Acetic acid, [[1'-[N-[N-[(1,1-dimethylethoxy)carbonyl]-2-methylalanyl]-O-(phenylmethyl)-D-seryl]spiro[3H-indole-3,4'-piperidin]-1(2H)-yl]sulfonyl]-, 6-[[5-(hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl)-1-oxopentyl]amino]hexyl ester, [3aS-(3a.alpha.,4.beta.,6a.alpha.)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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L28          10 SEA FILE=MEDLINE ABB=ON  RAT?(W)?ALDEHYDE?(W)?DEHYDROGENAS?

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L28  ANSWER 1 OF 10     MEDLINE on STN
ACCESSION NUMBER:   2003174023     MEDLINE
DOCUMENT NUMBER:    22578633   PubMed ID: 12691756
TITLE:              Peptide library approach with a disulfide tether to refine
                    the Tom20 recognition motif in mitochondrial presequences.
AUTHOR:             Obita Takayuki; Muto Takanori; Endo Toshiya; Kohda Daisuke
CORPORATE SOURCE:   Department of Structural Biology, Biomolecular Engineering
                    Research Institute, Suita, Osaka 565-0874, Japan.
SOURCE:             JOURNAL OF MOLECULAR BIOLOGY, (2003 Apr 25) 328 (2)
                    495-504.
                    Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY:       England: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200305
ENTRY DATE:         Entered STN: 20030416
                    Last Updated on STN: 20030524
                    Entered Medline: 20030523
AB   Many mitochondrial matrix and inner-membrane proteins are synthesized in
     the cytosol as precursor proteins with an N-terminal presequence, and are
     imported into the mitochondria. Although no distinct sequence homology
     has been found among mitochondrial presequences, Tom20, a general import
     receptor in the outer mitohcondrial membrane, binds to presequences, and
     distinguishes mitochondrial proteins from non-mitochonrial proteins. The
     recently determined structure of the cytosolic domain of Tom20
     (DeltaTom20) in a complex with the presequence of rat
     aldehyde dehydrogenase (ALDH) showed that a short
     stretch of the presequence forms an amphiphilic helix, and its hydrophobic
     surface interacts with the hydrophobic-binding groove of Tom20. The
     following NMR analyses revealed a common five-residue pattern for Tom20
     binding in five different presequences. To refine the common amino acid
     motif for the recognition by Tom20, we introduced a new peptide library
     approach in this study: we prepared a mixture of ALDH presequence
     variants, tethered these peptides to DeltaTom20 in a competitive manner by
     an intermolecular disulfide bond, and determined the relative affinities
     by MALDI-TOF mass spectrometry. We successfully deduced a refined, common
     motif for the recognition by Tom20, and found that the segment consisting
     of residues 14-20 of the ALDH presequence was locally optimized in the
     sequence space, with respect to Tom20 binding.
     Copyright 2003 Elsevier Science Ltd.

L28  ANSWER 2 OF 10     MEDLINE on STN
ACCESSION NUMBER:   2000185067     MEDLINE
DOCUMENT NUMBER:    20185067   PubMed ID: 10721992
TITLE:              Structural basis of presequence recognition by the
                    mitochondrial protein import receptor Tom20.
AUTHOR:             Abe Y; Shodai T; Muto T; Mihara K; Torii H; Nishikawa S;
                    Endo T; Kohda D
CORPORATE SOURCE:   Department of Structural Biology, Biomolecular Engineering
                    Research Institute, Suita, Osaka, Japan.
SOURCE:             CELL, (2000 Mar 3) 100 (5) 551-60.
                    Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY:       United States
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DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1OM2
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403

AB Most mitochondrial proteins are synthesized in the cytosol as precursor proteins with a cleavable N-terminal presequence and are imported into mitochondria. We report here the NMR structure of a general import receptor, rat Tom20, in a complex with a presequence peptide derived from **rat aldehyde dehydrogenase.** The cytosolic domain of Tom20 forms an all alpha-helical structure with a groove to accommodate the presequence peptide. The bound presequence forms an amphiphilic helical structure with hydrophobic leucines aligned on one side to interact with a hydrophobic patch in the Tom20 groove. Although the positive charges of the presequence are essential for import ability, presequence binding to Tom20 is mediated mainly by hydrophobic rather than ionic interactions.

L28 ANSWER 3 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2000167222 MEDLINE
DOCUMENT NUMBER: 20167222 PubMed ID: 10702312
TITLE: Molecular and biochemical characterization of rat gamma-trimethylaminobutyraldehyde dehydrogenase and evidence for the involvement of human aldehyde dehydrogenase 9 in carnitine biosynthesis.
AUTHOR: Vaz F M; Fouchier S W; Ofman R; Sommer M; Wanders R J
CORPORATE SOURCE: Laboratory for Genetic Metabolic Diseases, Departments of Clinical Chemistry and Pediatrics, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, P. O. Box 22700, 1100 DE Amsterdam, The Netherlands.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Mar 10) 275 (10) 7390-4.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF170918; GENBANK-AF170919; GENBANK-AF172093
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20021218
Entered Medline: 20000403

AB The penultimate step in carnitine biosynthesis is mediated by gamma-trimethylaminobutyraldehyde dehydrogenase (EC 1.2.1.47), a cytosolic NAD(+)-dependent aldehyde dehydrogenase that converts gamma-trimethylaminobutyraldehyde into gamma-butyrobetaine. This enzyme was purified from rat liver, and two internal peptide fragments were sequenced by Edman degradation. The peptide sequences were used to search the Expressed Sequence Tag data base, which led to the identification of a rat cDNA containing an open reading frame of 1485 base pairs encoding a polypeptide of 494 amino acids with a calculated molecular mass of 55 kDa. Expression of the coding sequence in Escherichia coli confirmed that the cDNA encodes gamma-trimethylaminobutyraldehyde dehydrogenase. The previously identified human aldehyde dehydrogenase 9 (EC 1.2.1.19) has 92% identity with **rat trimethylaminobutyraldehyde dehydrogenase** and has been reported to convert substrates that resemble gamma-trimethylaminobutyraldehyde. When aldehyde dehydrogenase 9

was expressed in E. coli, it exhibited high trimethylaminobutyraldehyde dehydrogenase activity. Furthermore, comparison of the enzymatic characteristics of the heterologously expressed human and rat dehydrogenases with those of purified rat liver trimethylaminobutyraldehyde dehydrogenase revealed that the three enzymes have highly similar substrate specificities. In addition, the highest V(max)/K(m) values were obtained with gamma-trimethylaminobutyraldehyde as substrate. This indicates that human aldehyde dehydrogenase 9 is the gamma-trimethylaminobutyraldehyde dehydrogenase, which functions in carnitine biosynthesis.

L28 ANSWER 4 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2000014014 MEDLINE
DOCUMENT NUMBER: 20014014 PubMed ID: 10548037
TITLE: Differences in the roles of conserved glutamic acid residues in the active site of human class 3 and class 2 aldehyde dehydrogenases.
AUTHOR: Mann C J; Weiner H
CORPORATE SOURCE: Department of Biochemistry, Purdue University, West Lafayette, Indiana 47907-1153, USA.
CONTRACT NUMBER: AA05812 (NIAAA)
SOURCE: PROTEIN SCIENCE, (1999 Oct) 8 (10) 1922-9.
Journal code: 9211750. ISSN: 0961-8368.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000211

AB Although the three-dimensional structure of the dimeric class 3 **rat aldehyde dehydrogenase** has recently been published (Liu ZJ et al., 1997, Nature Struct Biol 4:317-326), few mechanistic studies have been conducted on this isoenzyme. We have characterized the enzymatic properties of recombinant class 3 human stomach aldehyde dehydrogenase, which is very similar in amino acid sequence to the class 3 **rat aldehyde dehydrogenase**. We have determined that the rate-limiting step for the human class 3 isozyme is hydride transfer rather than deacylation as observed for the human liver class 2 mitochondrial enzyme. No enhancement of NADH fluorescence was observed upon binding to the class 3 enzyme, while fluorescence enhancement of NADH has been previously observed upon binding to the class 2 isoenzyme. It was also observed that binding of the NAD cofactor inhibited the esterase activity of the class 3 enzyme while activating the esterase activity of the class 2 enzyme. Site-directed mutagenesis of two conserved glutamic acid residues (209 and 333) to glutamine residues indicated that, unlike in the class 2 enzyme, Glu333 served as the general base in the catalytic reaction and E209Q had only marginal effects on enzyme activity, thus confirming the proposed mechanism (Hempel J et al., 1999, Adv Exp Med Biol 436:53-59). Together, these data suggest that even though the subunit structures and active site residues of the isozymes are similar, the enzymes have very distinct properties besides their oligomeric state (dimer vs. tetramer) and substrate specificity.

L28 ANSWER 5 OF 10 MEDLINE on STN
ACCESSION NUMBER: 1999201470 MEDLINE
DOCUMENT NUMBER: 99201470 PubMed ID: 10101022
TITLE: The negative regulation of the **rat**

aldehyde dehydrogenase 3 gene by glucocorticoids: involvement of a single imperfect palindromic glucocorticoid responsive element.

AUTHOR: Falkner K C; Xiao G H; Pinaire J A; Pendleton M L; Lindahl R; Prough R A
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Louisville School of Medicine, Louisville, Kentucky 40292, USA.
CONTRACT NUMBER: CA21103 (NCI)
RO1-ES04244 (NIEHS)
SOURCE: MOLECULAR PHARMACOLOGY, (1999 Apr) 55 (4) 649-57.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990504
Last Updated on STN: 19990504
Entered Medline: 19990420

AB Glucocorticoids repressed the polycyclic aromatic hydrocarbon-dependent induction of Class 3 aldehyde dehydrogenase (ALDH3) enzyme activity and mRNA levels in isolated rat hepatocytes by more than 50 to 80%, with a concentration-dependence consistent with the involvement of the glucocorticoid receptor (GR). No consistent effect on the low basal transcription rate was observed. This effect of glucocorticoids (GC) on polycyclic aromatic hydrocarbon induction was effectively antagonized at the mRNA and protein level by the GR antagonist RU38486. The response was cycloheximide-sensitive, because the protein synthesis inhibitor caused a GC-dependent superinduction of ALDH3 mRNA levels. This suggests that the effects of GC on this gene are complex and both positive and negative gene regulation is possible. The GC-response was recapitulated in HepG2 cells using transient transfection experiments with CAT reporter constructs containing 3.5 kb of 5'-flanking region from ALDH3. This ligand-dependent response was also observed when a chimeric GR (GR DNA-binding domain and peroxisome proliferator-activated receptor ligand-binding domain) was used in place of GR in the presence of the peroxisome proliferator, nafenopin. A putative palindromic glucocorticoid-responsive element exists between -930 and -910 base pairs relative to the transcription start site. If this element was either deleted or mutated, the negative GC-response was completely lost, which suggests that this sequence is responsible, in part, for the negative regulation of the gene. Electrophoretic mobility shift analysis demonstrated that this palindromic glucocorticoid-responsive element is capable of forming a specific DNA-protein complex with human glucocorticoid receptor. In conclusion, the negative regulation of ALDH3 in rat liver is probably mediated through direct GR binding to its canonical responsive element.

L28 ANSWER 6 OF 10 MEDLINE on STN
ACCESSION NUMBER: 97166161 MEDLINE
DOCUMENT NUMBER: 97166161 PubMed ID: 9013560
TITLE: cAMP-dependent negative regulation of **rat aldehyde dehydrogenase** class 3 gene expression.
AUTHOR: Xiao G h; Falkner K C; Xie Y; Lindahl R G; Prough R A
CORPORATE SOURCE: Department of Biochemistry, School of Medicine, University of Louisville, Louisville, Kentucky 40292, USA.
CONTRACT NUMBER: CA 21103 (NCI)
R01 ES04244 (NIEHS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Feb 7) 272 (6)

3238-45.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970414
Last Updated on STN: 19980206
Entered Medline: 19970402

AB We investigated the inhibitory effects of intracellular cyclic adenosine monophosphate (cAMP) levels in regulating class 3 aldehyde dehydrogenase (aldh3) gene expression using cultures of primary rat hepatocytes and transient transfection experiments with HepG2 cells. In addition to regulation by an Ah receptor-dependent mechanism, expression of many members of the Ah gene battery have been shown to be negatively regulated. As was seen for the cytochrome P450 (cyp1A1) gene, aldh3 is transcriptionally inducible by polycyclic aromatic hydrocarbons (PAH), and this induction involving function of the arylhydrocarbon (Ah) receptor is inhibited by the protein kinase C (PKC) inhibitors, 1-(5-isoquinolinesulfonyl)-2-methylpiperazine di-HCl (H7) and staurosporine. However, PAH induction of ALDH-3 activity, protein, and mRNA was potentiated 2-4-fold by addition of the protein kinase A (PKA) inhibitors, N-(2-(methylamino)ethyl)-5-isoquinolinesulfonamide di-HCl (H8) and N-(2-guanidinoethyl)-5-isoquinolinesulfonamide HCl (HA1004). These PKA inhibitors had no effect on the PAH induction of the cyp1A1. Protein kinase A activity of cultured hepatocytes was specifically inhibited by H8 and HA1004 in a concentration-dependent manner, but not by H7, and there was an inverse correlation observed between potentiation of PAH-induced aldh3 gene expression and inhibition of specific PKA activity by the PKA inhibitors. The cAMP analog dibutyryl cAMP, the adenylate cyclase activator forskolin, and the protein phosphatase 1 and 2A inhibitor okadaic acid all dramatically inhibited both PAH induction and H8 potentiation of PAH induction of aldh3 expression but had no effect on induction of cyp1A1 expression in cultured hepatocytes. Both basal and PAH-dependent expression of a chloramphenicol acetyltransferase expression plasmid containing approximately 3.5 kilobase pairs of the 5'-flanking region of aldh3 (pALDH3.5CAT) were enhanced 3-4-fold by the PKA inhibitor H8 but not by the PKC inhibitor H7 (>20 microM). cAMP analogs, activators of PKA activity, or protein phosphatase inhibitors diminished expression of the reporter gene in a manner identical to the native gene in cultured rat hepatocytes. Using deletion analysis of the pALDH3.5CAT construct, we demonstrated the existence of a negative regulatory region in the 5'-flanking region between -1057 and -991 base pairs which appears to be responsible for the cAMP-dependent regulation of this gene under both basal and PAH-induced conditions. At least two apparently independent mechanisms which involve protein phosphorylation regulate aldh3 expression. One involves function of the Ah receptor which requires PKC protein phosphorylation to positively regulate both aldh3 and cyp1A1 gene expression and the other a cAMP-responsive process which allows PKA activity to negatively regulate expression of aldh3 under either basal or inducible conditions.

L28 ANSWER 7 OF 10 MEDLINE on STN
ACCESSION NUMBER: 96125208 MEDLINE
DOCUMENT NUMBER: 96125208 PubMed ID: 8543180
TITLE: Cloning of a cDNA encoding **rat aldehyde dehydrogenase** with high activity for retinal oxidation.
AUTHOR: Bhat P V; Labrecque J; Boutin J M; Lacroix A; Yoshida A

CORPORATE SOURCE: Laboratory of Nutrition and Cancer, Hotel-Dieu de Montreal, Quebec, Canada.
SOURCE: GENE, (1995 Dec 12) 166 (2) 303-6.
Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L42009
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960227
Last Updated on STN: 19960227
Entered Medline: 19960212

AB Retinoic acid (RA), an important regulator of cell differentiation, is biosynthesized from retinol via retinal by a two-step oxidation process. We previously reported the purification and partial amino acid (aa) sequence of a rat kidney aldehyde dehydrogenase (ALDH) isozyme that catalyzed the oxidation of 9-cis and all-trans retinal to corresponding RA with high efficiency [Labrecque et al. Biochem. J. 305 (1995) 681-684]. A rat kidney cDNA library was screened using a 291-bp PCR product generated from total kidney RNA using a pair of oligodeoxyribonucleotide primers matched with the aa sequence. The full-length rat kidney ALDH cDNA contains a 2315-bp (501 aa) open reading frame (ORF). The aa sequence of rat kidney ALDH is 89, 96 and 87% identical to that of the rat cytosolic ALDH, the mouse cytosolic ALDH and human cytosolic ALDH, respectively. Northern blot and RT-PCR-mediated analysis demonstrated that rat kidney ALDH is strongly expressed in kidney, lung, testis, intestine, stomach and trachea, but weakly in the liver.

L28 ANSWER 8 OF 10 MEDLINE on STN
ACCESSION NUMBER: 91333229 MEDLINE
DOCUMENT NUMBER: 91333229 PubMed ID: 1870355
TITLE: Action of metadoxine on isolated human and rat alcohol and aldehyde dehydrogenases. Effect on enzymes in chronic ethanol-fed rats.
AUTHOR: Pares X; Moreno A; Peralba J M; Font M; Bruseghini L; Esteras A
CORPORATE SOURCE: Departament de Bioquimica i Biologia Molecular, Facultat de Ciencies, Universitat Autonoma de Barcelona, Spain.
SOURCE: METHODS AND FINDINGS IN EXPERIMENTAL AND CLINICAL PHARMACOLOGY, (1991 Jan-Feb) 13 (1) 37-42.
Journal code: 7909595. ISSN: 0379-0355.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199109
ENTRY DATE: Entered STN: 19911006
Last Updated on STN: 19970203
Entered Medline: 19910913

AB Metadoxine (pyridoxine-pyrrolidone carboxylate) has been reported to accelerate ethanol metabolism. In the present work we have investigated the effect of metadoxine on the activities of isolated alcohol and aldehyde dehydrogenases from rat and man, and on the activity of these enzymes in chronic ethanol-fed rats. Our results indicate that in vitro metadoxine does not activate any of the enzymatic forms of alcohol dehydrogenase (classes I and II) or aldehyde dehydrogenase (low-Km and high-Km, cytosolic and mitochondrial). At concentrations higher than 0.1 mM, metadoxine inhibits rat class II alcohol dehydrogenase, although this would probably not affect the physiological ethanol metabolism. Chronic

ethanol intake for 5 weeks results in a 25% decrease of rat hepatic alcohol dehydrogenase (class I) activity as compared with the pair-fed controls. The simultaneous treatment with metadoxine prevents activity loss, suggesting that the positive effect of metadoxine on ethanol metabolism can be explained by the maintenance of normal levels of alcohol dehydrogenase during chronic ethanol intake. No specific effect of chronic exposure to ethanol or to metadoxine was detected on **rat aldehyde dehydrogenase** activity.

L28 ANSWER 9 OF 10 MEDLINE on STN
ACCESSION NUMBER: 91254350 MEDLINE
DOCUMENT NUMBER: 91254350 PubMed ID: 2043148
TITLE: Lipid aldehyde oxidation as a physiological role for class 3 aldehyde dehydrogenases.
AUTHOR: Lindahl R; Petersen D R
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of South Dakota, School of Medicine, Vermillion 57069.
CONTRACT NUMBER: AA 06985 (NIAAA)
AA03527 (NIAAA)
CA 21103 (NCI)
+
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1991 Jun 1) 41 (11) 1583-7.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199107
ENTRY DATE: Entered STN: 19910728
Last Updated on STN: 19970203
Entered Medline: 19910710

AB A large number of different unsaturated, saturated and hydroxylated aliphatic aldehydes can be generated during the peroxidation of cellular lipids. This study examined the kinetic properties of purified Class 3 **rat aldehyde dehydrogenase** (ALDH) with respect to the oxidation of various lipid aldehyde substrates. It also compared the substrate preference of the prototypic Class 3 ALDH with that of the constitutive rat microsomal aldehyde dehydrogenase. The results suggest that (1) microsomal ALDH is a member of the Class 3 aldehyde dehydrogenase family, and (2) the physiological role of the Class 3 ALDHs, including the microsomal form, is the oxidation of medium (6 to 9 carbon) chain length saturated and unsaturated aldehydes generated by the peroxidation of cellular lipids. Short chain aliphatic aldehydes, such as a malondialdehyde and 4-hydroxyalkenals, are not substrates for the Class 3 aldehyde dehydrogenases.

L28 ANSWER 10 OF 10 MEDLINE on STN
ACCESSION NUMBER: 91200666 MEDLINE
DOCUMENT NUMBER: 91200666 PubMed ID: 2016061
TITLE: Bovine corneal protein 54K (BCP54) is a homologue of the tumor-associated (class 3) **rat aldehyde dehydrogenase** (RATALD).
AUTHOR: Cooper D L; Baptist E W; Enghild J J; Isola N R; Klintworth G K
CORPORATE SOURCE: Department of Pathology, Duke University, Durham, NC 27710.
SOURCE: GENE, (1991 Feb 15) 98 (2) 201-7.
Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M37384; GENBANK-M37851; GENBANK-M37852; GENBANK-M63445; GENBANK-M74185; GENBANK-S75878; GENBANK-X52535; GENBANK-X52536; GENBANK-X52537; GENBANK-X52538
ENTRY MONTH: 199105
ENTRY DATE: Entered STN: 19910607
Last Updated on STN: 20000303
Entered Medline: 19910521

AB Amino acid (aa) sequence data from Staphylococcus areas V8 protease-digested bovine corneal 54-kDa protein (BCP54) fragments were utilized to derive mixed oligodeoxyribonucleotide (oligo) primers complementary to the reverse translation products of these sequences. These degenerate oligo primers were used to prime the amplification of BCP54 sequence from bovine corneal epithelial cell cDNA. The cDNA probe generated by this mixed oligo-primed amplification of cDNA was cloned and dideoxy-sequenced. A search of the GenBank database (version 63.0) revealed extensive sequence similarity to the cDNA encoding tumor-associated rat liver (class 3) aldehyde dehydrogenase (RATALD). Nucleotide (nt) and aa sequence alignment of the BCP54 translation product reveals it is 78% and 84% homologous with RATALD at the nt and aa levels, respectively. Conservation of aa sequence elements common to the aldehyde dehydrogenase family thought to be of structural/functional significance is further substantiated by this analysis. Included in the discussion is the likelihood that gene sharing (genes encoding metabolic enzymes and other stable proteins) may extend to the cornea.